

FIGURE 1

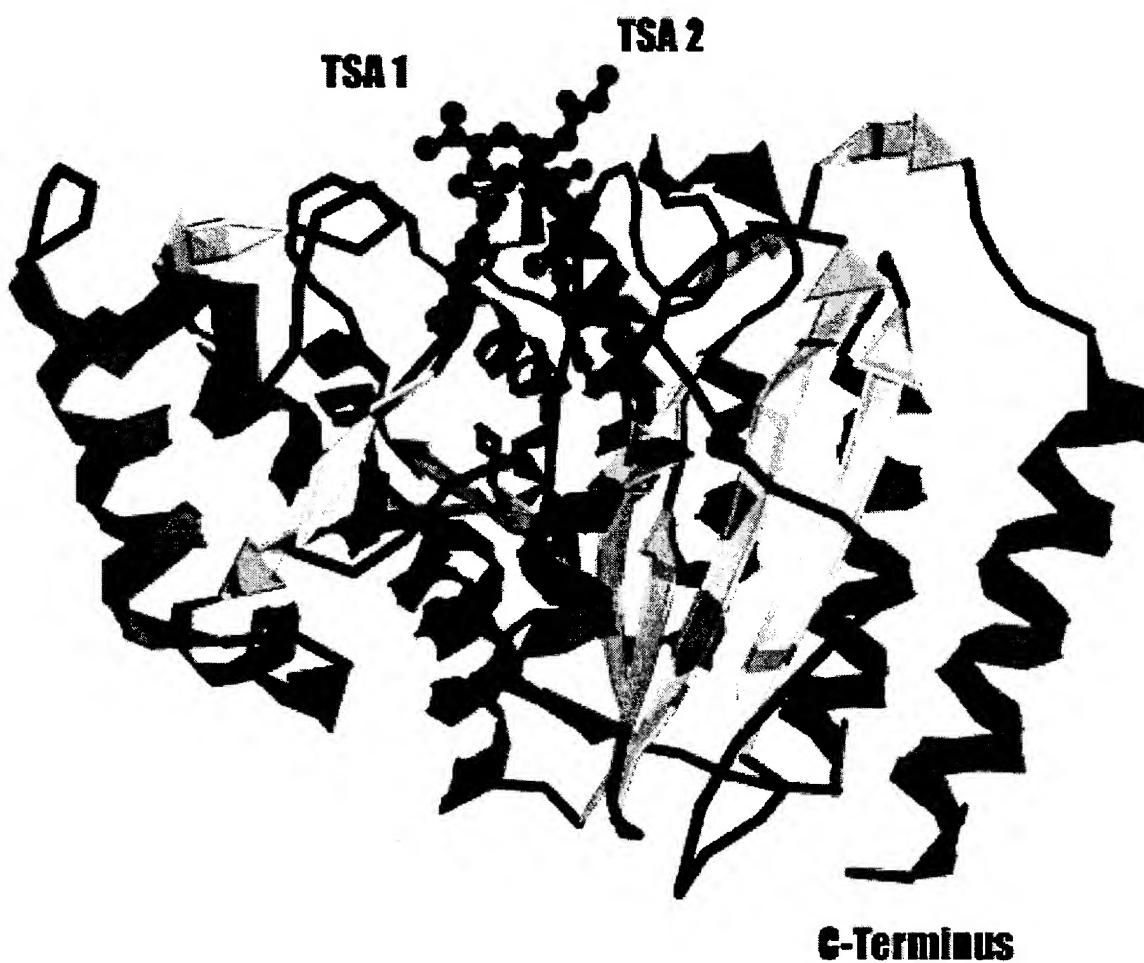


FIGURE 2A

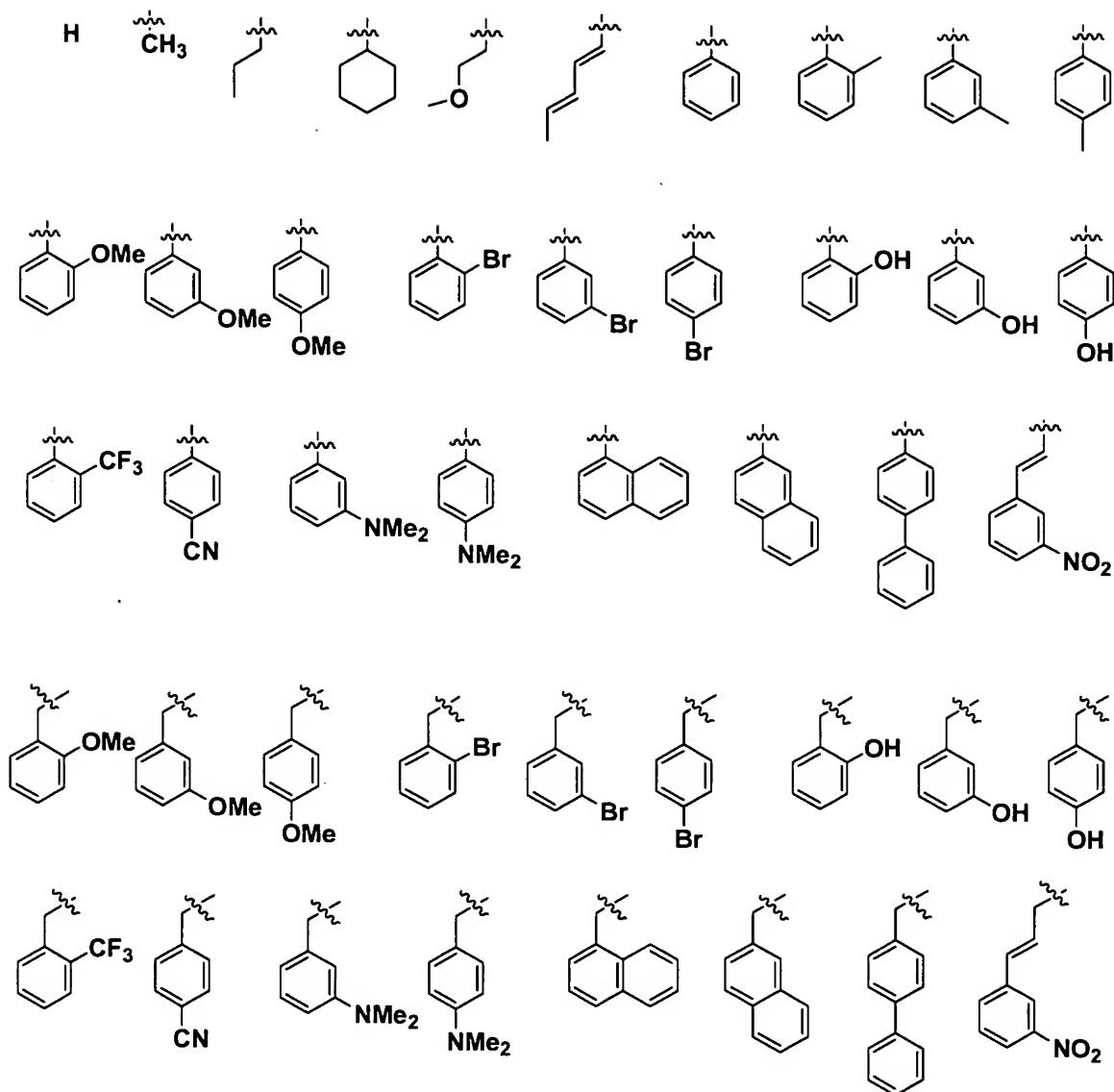


FIGURE 2A (cont.)

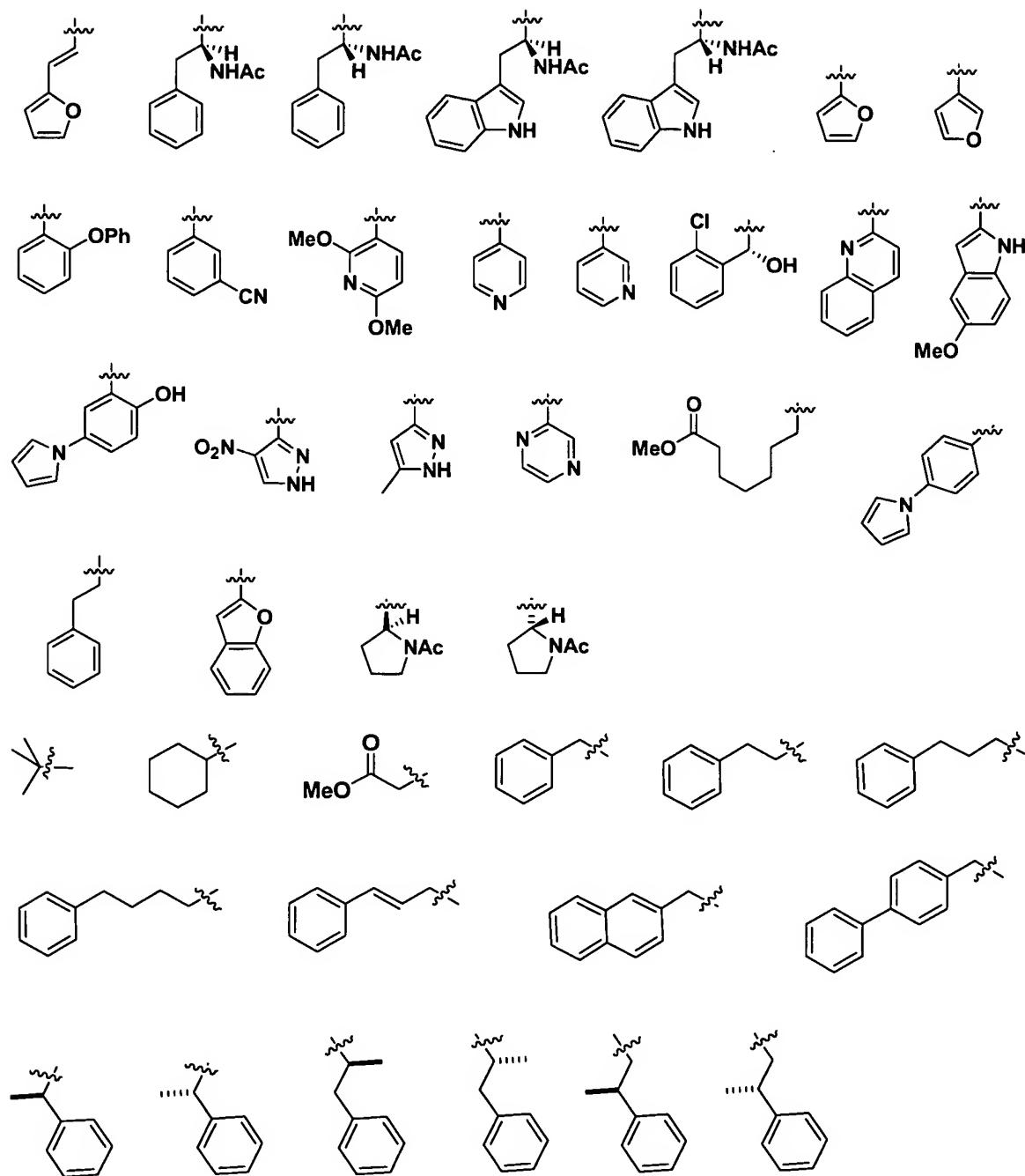


FIGURE 2A (cont.)

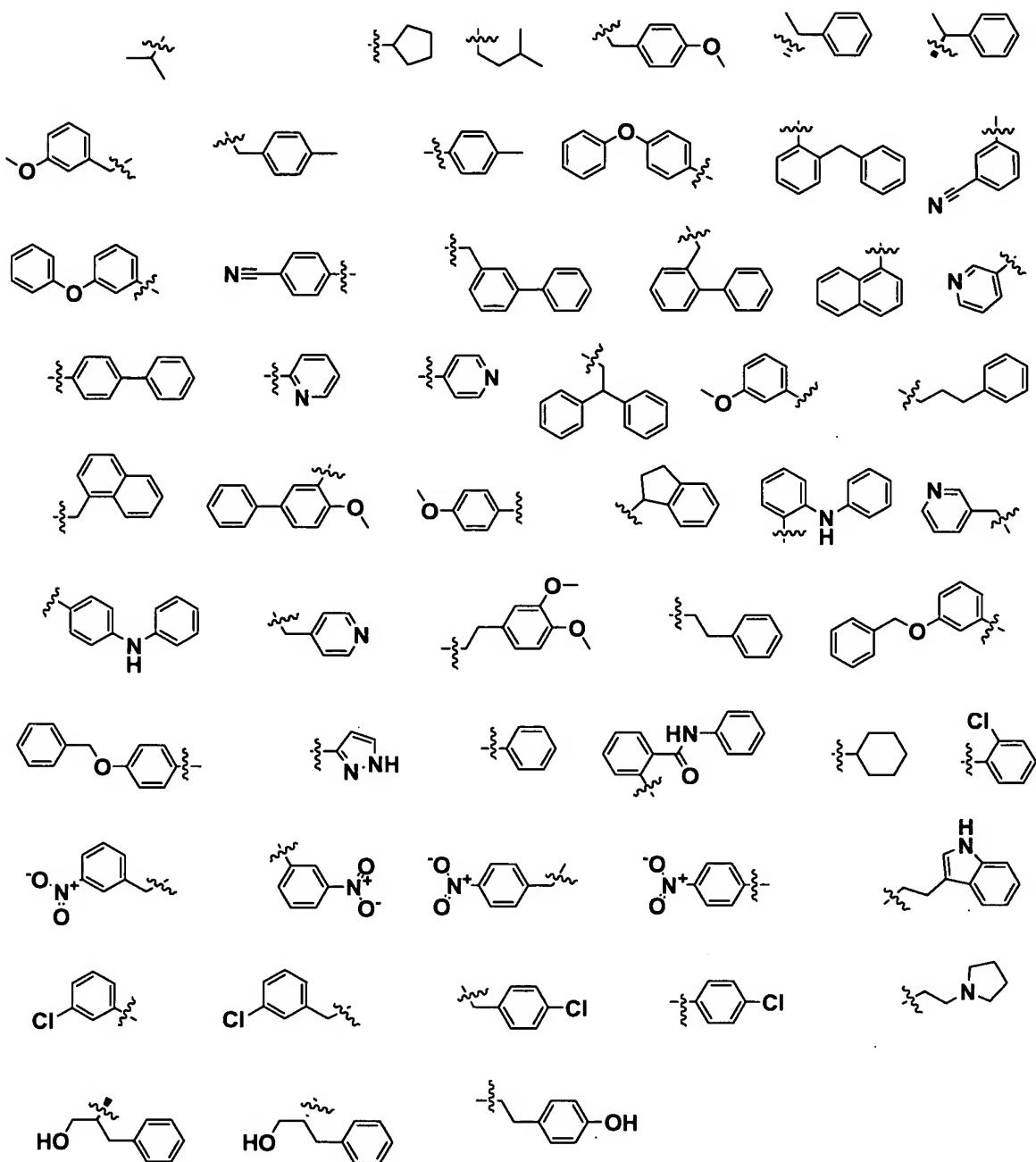


FIGURE 2B

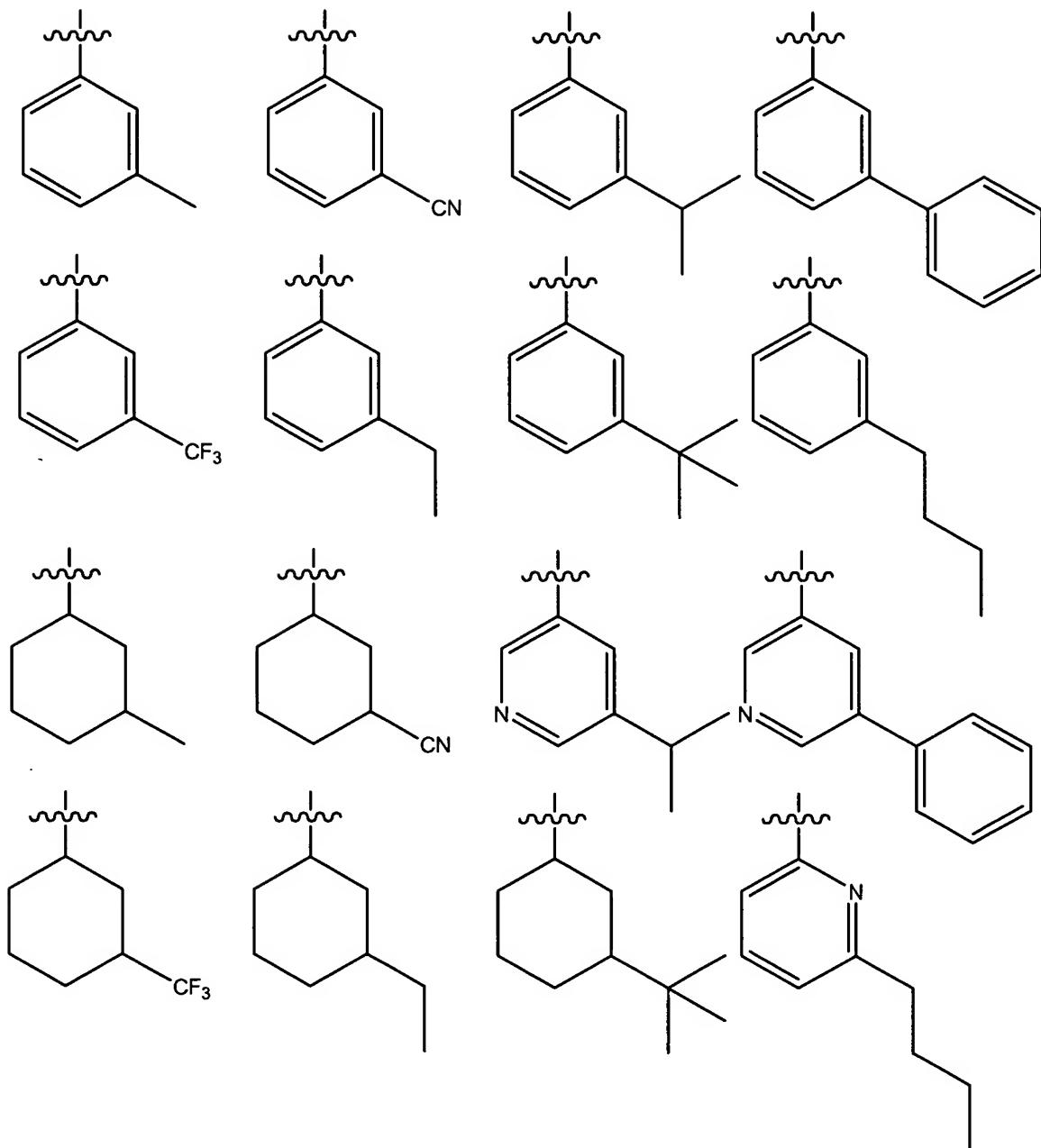


FIGURE 2B (cont.)

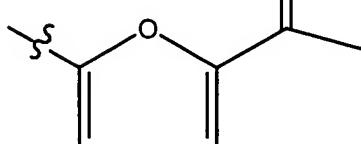
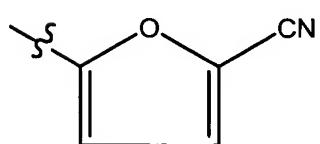
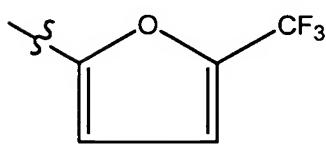
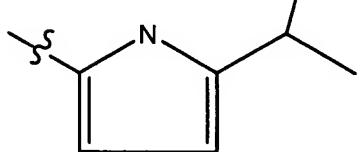
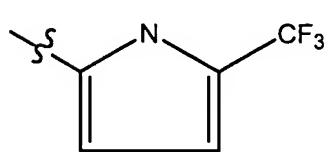
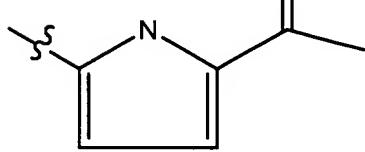
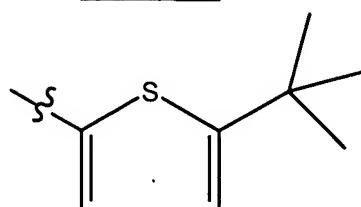
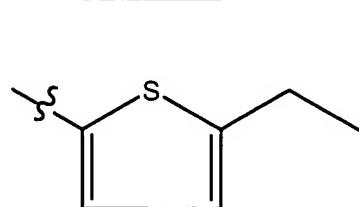
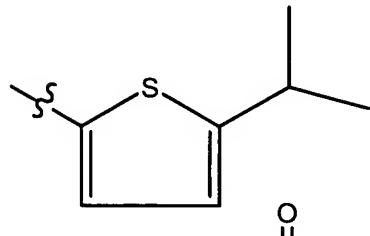
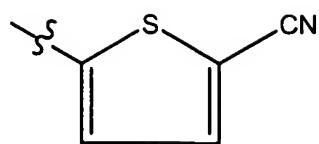
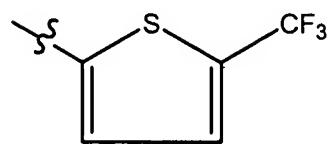
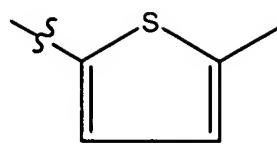


FIGURE 2B (cont.)

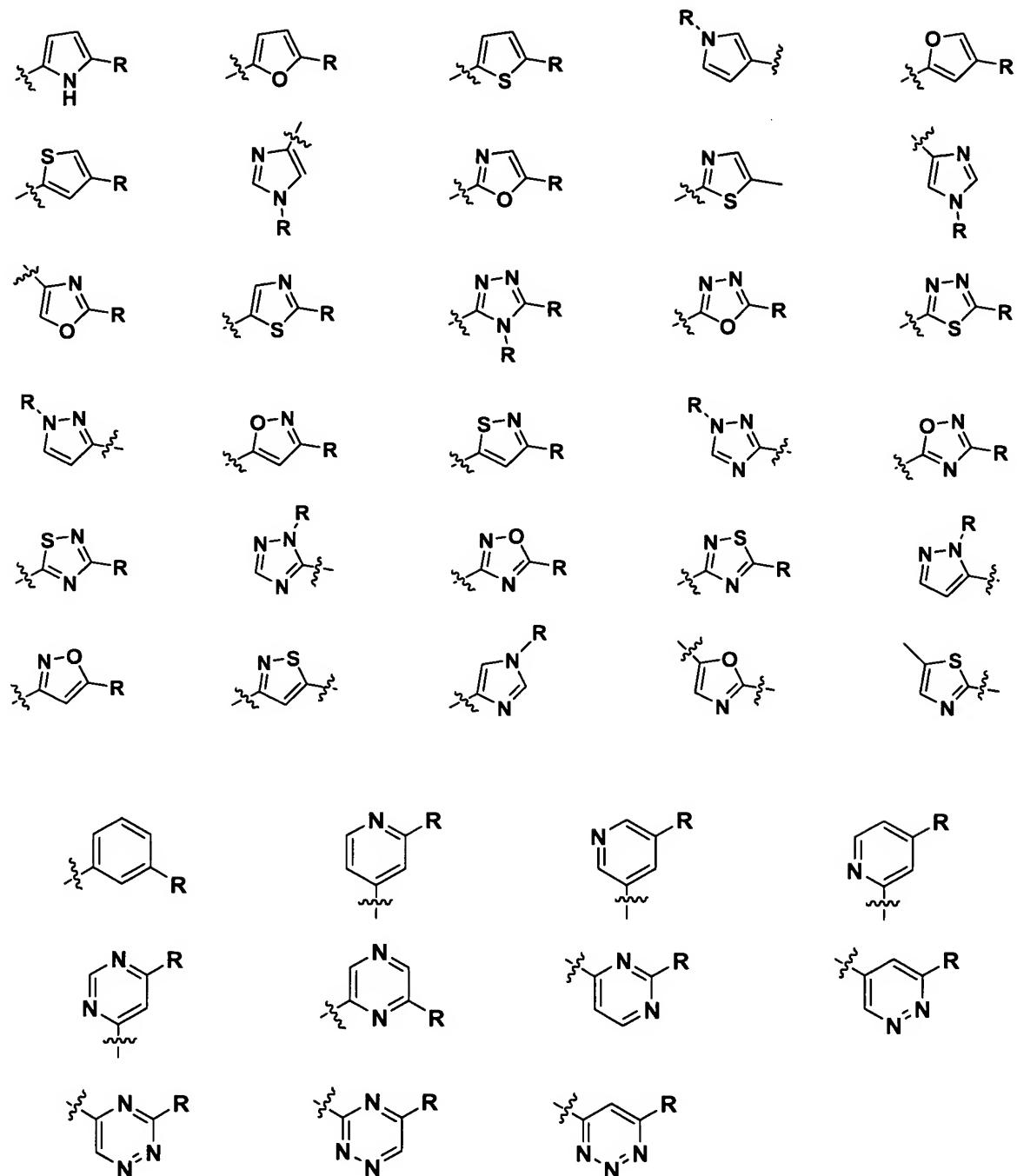


FIGURE 2C

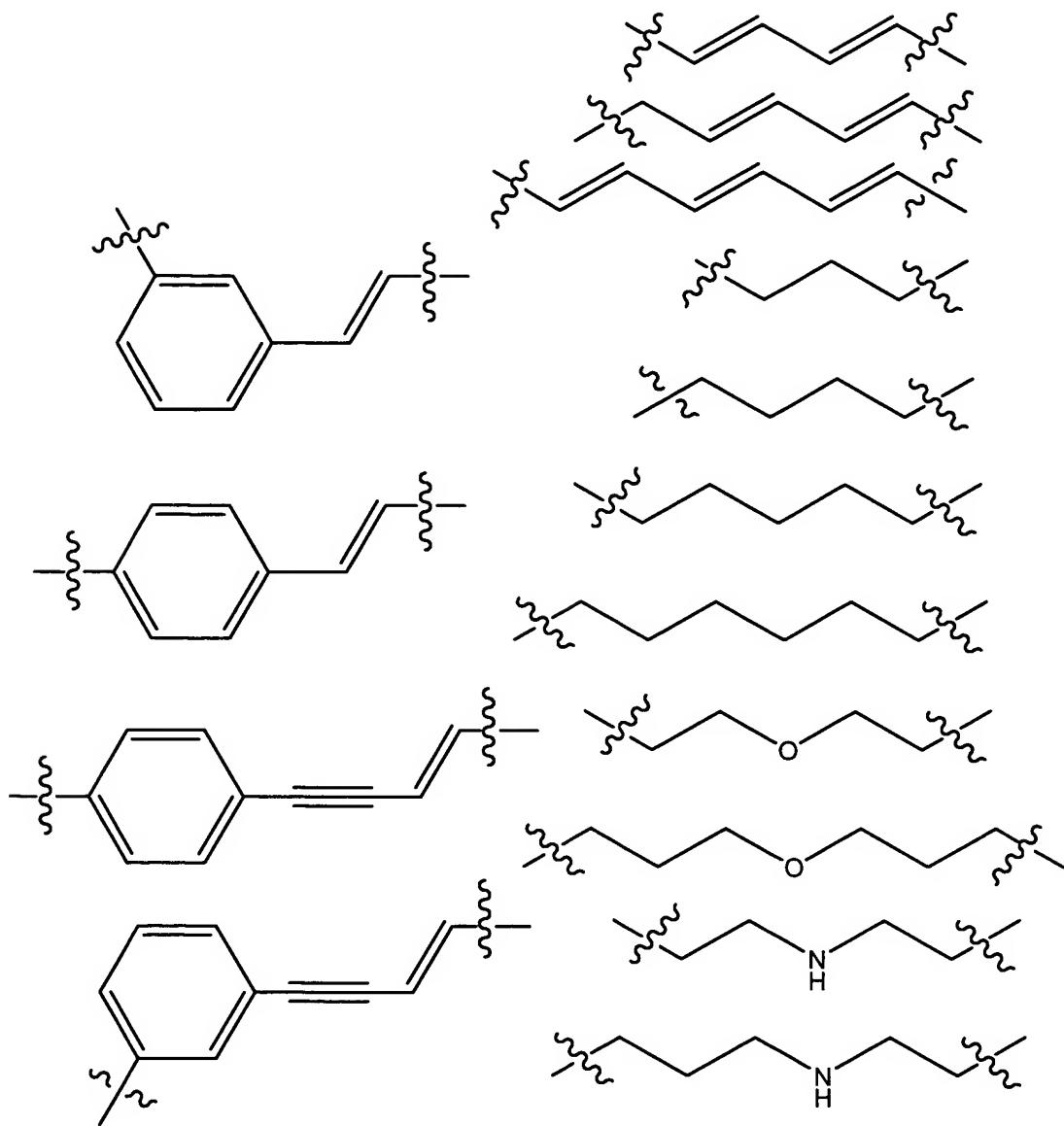


FIGURE 2C (cont.)

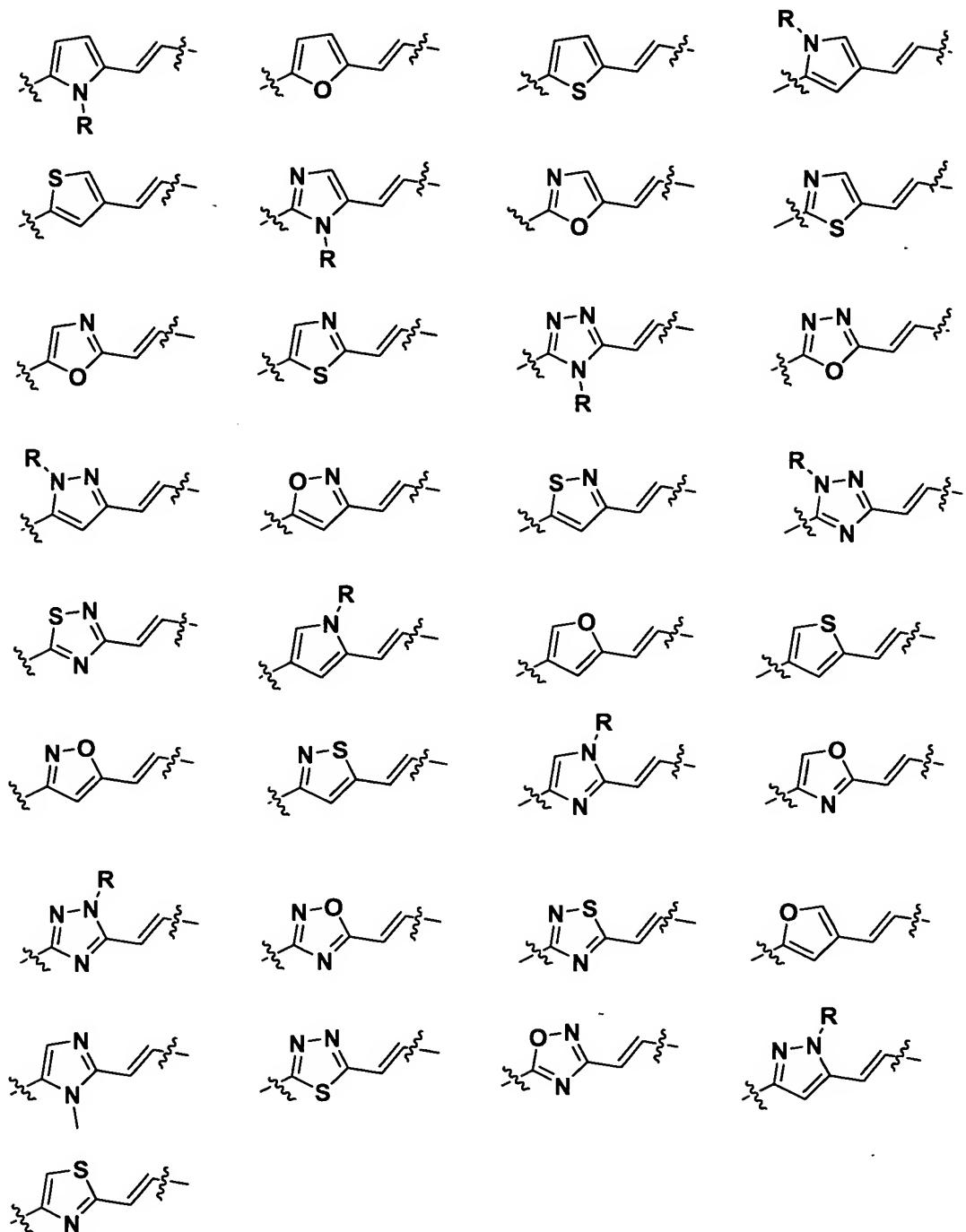


FIGURE 2C (cont.)

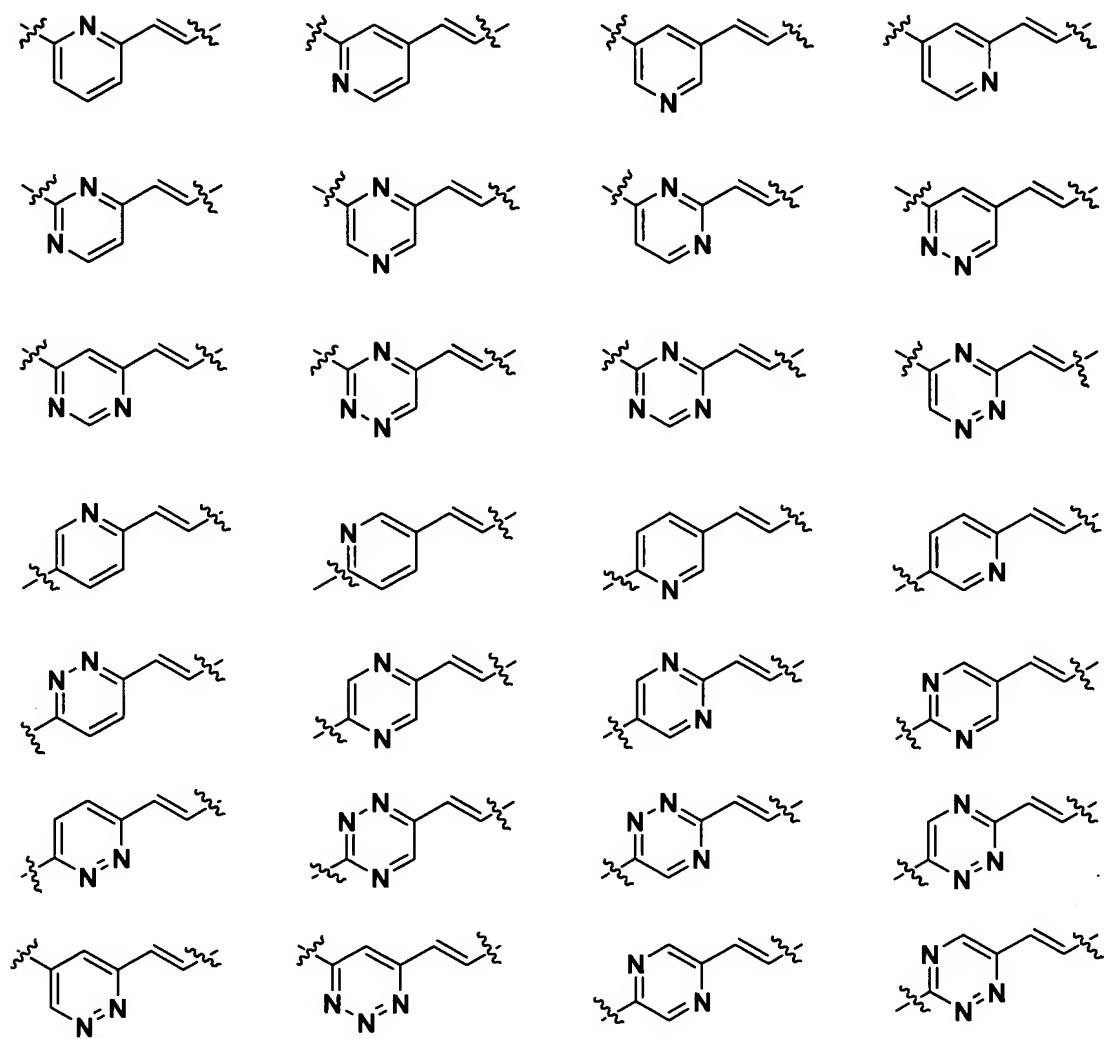


FIGURE 3

Amino acid sequence for full length human wild type HDAC8 [SEQ. ID No. 1]

MEEPEEPADSGQSLVPVYIYSPEYVSMCDSLAKIPKRASMVHSLIEAYALHKQM RIVKPK 60
VASMEEMATFHTDAYLQHLQKV S QEGDDDHPDSIEYGLGYDCPATEGIFDYAAAIGGATI 120
TAAQCLIDGMCKVAINWSGGWHHAKKDEASGFCYLNDAVLGILRLRRKFERILYVDLDH 180
HGDGVEDA FSFTSKVMTVSLHKFSPGFFPGTGDVSDVGLGKGWYY SVNVP IQDGIQDEKY 240
YQICESVLKEVYQAFNPKA VVLQLGADTIAGDPMCSFN MTPVVGIGKCLKYI LQWQLATLI 300
LGGGGYNLANTARCWTYLTGVILGKTL SSEIPDHEFFTAYGPDYVLEITPSCR PDRNEPH 360
RIQQILNYIKGNLKHVV 377

Human cDNA sequence HDAC8 [SEQ. ID No. 2]

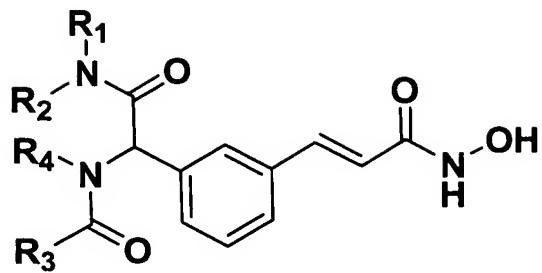
ATGGAGGAGCCGGAGGAACCGGGACAGTGGCAGTCGCTGGTCCCGTTATATCTAT 60
AGTCCCAGATGTCAGTATGTGTGACTCCCTGGCAAGATCCCCAAACGGGCCAGTATG 120
GTGCATTCTTGATTGAAGCATATGCACTGCATAAGCAGATGAGGATAGTTAACGCTAA 180
GTGGCCTCCATGGAGGAGATGGCACCTTCCACACTGATGCTTATCTGCAGCATCTCCAG 240
AAGGTCA GCCAAGAGGGCGATGATGATCATCCGACTCCATAGAATATGGCTAGGTTAT 300
GA CTGCCCAGCCACTGAAGGGATATTGACTATGCAGCAGCTATAGGAGGGCTACGATC 360
ACAGCTGCCAATGCCTGATTGACGGAATGTGCAAAGTAGCAATTAACTGGTCTGGAGGG 420
TGGCATCATGCAAAGAAAGATGAAGCATCTGGTTTTGTTATCTCAATGATGCTGTCCTG 480
GGAATATTACGATTGCGACGGAAATTGAGCGTATTCTACGTGGATTGATCTGCAC 540
CATGGAGATGGTGTAGAAGACGCATTCA GTTCACCTCCAAAGTCATGACCGTGTCCCTG 600
CACA AATTCTCCCCAGGATT TCCCAGGAACAGGTGACGTGTGATGTTGGCCTAGGG 660
AAGGGATGGTACTACAGTGTAAATGTGCCATTCA CAGGATGGCATACAAGATGAAAATAT 720
TACCA GATCTGTGAAAGCGTACTAAAGGAAGTATA CCACAGCCTTAATCCCAAAGCAGTG 780
GTCTTACAGCTGGAGCTGACACAATAGCTGGGATCCCATGTGCTCTTAA CATGACT 840
CCAGTGGGAATTGGCAAGTGTCTTAAGTACATCCTCAATGGCAGTTGGCAACACTCATT 900
TTGGGAGGAGGAGGAGGCTATAACCTGCCAACACGGCTCGATGCTGGACATACTGACCGGG 960
GTCATCCTAGGGAAAACACTATCCTCTGAGATCCCAGATCATGAGTTTACAGCATAT 1020
GGTCCTGATTATGTGCTGGAAATACGCCAAGCTGCCAGACCGCAATGAGCCCCAC 1080
CGAATCCAACAAATCCTCAACTACATCAAAGGGATCTGAAGCATGTGGCTAG 1134

FIGURE 4

Amino acid sequence for residues 1-377 of HDAC8 with a cleavable N-terminal 6x-histidine tag [SEQ. ID No. 3] (6x-histidine tag underlined)

MHHHHHHPMEEPEEPADSGQSLVPVYIYSPEYVSMCDSLAKIPKRASMVHSLIEAYALHK 60
QM RIVKPKV ASMEEMAA FHTDAYLQHLQKV S QEGDDDHPDSIEYGLGYDCPATEGIFDYA 120
AAIGGATITAAQCLIDGMCKVAINWSGGWHHAKKDEASGFCYLNDAVLGILRLRRKFERI 180
LYV DLDLHHGDGVEDA FSFTSKVMTVSLHKFSPGFFPGTGDVSDVGLGKGWYY SVNVP IQDGIQDEKY 240
DGIQDEKYYQICESVLKEVYQAFNPKA VVLQLGADTIAGDPMCSFN MTPVVGIGKCLKYI L 300
QWQLATLILGGGGYNLANTARCWTYLTGVILGKTL SSEIPDHEFFTAYGPDYVLEITPSC 360
RPDRNEPHRIQQILNYIKGNLKHVV 385

Figure 5A



R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	H	CH ₃	
PhCH ₂	H	CH ₃	CH ₃	
PhCH ₂	H	n-Propyl	CH ₃	
PhCH ₂	H	c-Hexyl	CH ₃	
PhCH ₂	H	MeO(CH ₂)-	CH ₃	
PhCH ₂	H	Me(CH=CH) ₂ -	CH ₃	
PhCH ₂	H	Ph	CH ₃	Yes
PhCH ₂	H	o-MePh	CH ₃	
PhCH ₂	H	m-MePh	CH ₃	
PhCH ₂	H	p-MePh	CH ₃	
PhCH ₂	H	o-CF ₃ Ph	CH ₃	
PhCH ₂	H	m-CF ₃ Ph	CH ₃	
PhCH ₂	H	p-CF ₃ Ph	CH ₃	
PhCH ₂	H	o-MeOPh	CH ₃	
PhCH ₂	H	m-MeOPh	CH ₃	
PhCH ₂	H	p-MeOPh	CH ₃	
PhCH ₂	H	o-BrPh	CH ₃	
PhCH ₂	H	m-BrPh	CH ₃	Yes
PhCH ₂	H	p-BrPh	CH ₃	
PhCH ₂	H	o-HOPh	CH ₃	
PhCH ₂	H	m-HOPh	CH ₃	
PhCH ₂	H	p-HOPh	CH ₃	
PhCH ₂	H	o-PhOPh	CH ₃	
PhCH ₂	H	m-PhOPh	CH ₃	Yes
PhCH ₂	H	p-PhOPh	CH ₃	Yes
PhCH ₂	H	m-Me ₂ NPh	CH ₃	
PhCH ₂	H	p-Me ₂ NPh	CH ₃	
PhCH ₂	H	m-NCPh	CH ₃	Yes
PhCH ₂	H	p-NCPh	CH ₃	
PhCH ₂	H	1-Naphthyl	CH ₃	Yes
PhCH ₂	H	1-Naphthylmethyl	CH ₃	Yes

Figure 5A (cont.)

R1	R2	R3	R4	< 5 μ M Activity
PhCH ₂	H	2-Naphthyl	CH ₃	Yes
PhCH ₂	H	p-PhPh	CH ₃	Yes
PhCH ₂	H	m-NO ₂ PhCH=CH-	CH ₃	
PhCH ₂	H	PhCH ₂ CH ₂ -	CH ₃	Yes
PhCH ₂	H	PhCH ₂	CH ₃	Yes
PhCH ₂	H	Ac-D-Pro	CH ₃	
PhCH ₂	H	Ac-L-Pro	CH ₃	
PhCH ₂	H	Ac-D-Phe	CH ₃	
PhCH ₂	H	Ac-L-Phe	CH ₃	
PhCH ₂	H	Ac-D-Try	CH ₃	
PhCH ₂	H	Ac-L-Try	CH ₃	
PhCH ₂	H	2-furyl	CH ₃	
PhCH ₂	H	3-furyl	CH ₃	
PhCH ₂	H	furylCH=CH-	CH ₃	
PhCH ₂	H	2-benzofuranyl	CH ₃	Yes
PhCH ₂	H	1-methyl-2-pyrrolyl	CH ₃	
PhCH ₂	H	4-(1H-pyrrol-1-yl)Ph	CH ₃	
PhCH ₂	H	2-hydroxy-5-(1H-pyrrol-1-yl)	CH ₃	
PhCH ₂	H	2,6-dimethoxypyridyl	CH ₃	
PhCH ₂	H	4-pyridyl	CH ₃	
PhCH ₂	H	3-pyridyl	CH ₃	
PhCH ₂	H	α -hydroxymethyl	CH ₃	
PhCH ₂	H	2-quinolinyl	CH ₃	Yes
PhCH ₂	H	5-methoxy-2-indolyl	CH ₃	
PhCH ₂	H	MeO ₂ C(CH ₂) ₆ -	CH ₃	Yes
PhCH ₂	H	4-nitro-3-pyrazolyl	CH ₃	
PhCH ₂	H	4-imidazolyl-CH=CH-	CH ₃	
PhCH ₂	H	(2-pyrimidylthio)CH ₂	CH ₃	
PhCH ₂	H	5-methyl-3-pyrazolyl	CH ₃	
PhCH ₂	H	3-hydroxy-2-quinoxaliny	CH ₃	
PhCH ₂	H	2-pyrazinyl	CH ₃	
PhCH ₂	H	H	CH ₃	
PhCH ₂	H	H	Isopropyl	Yes
PhCH ₂	H	H	Ethyl	

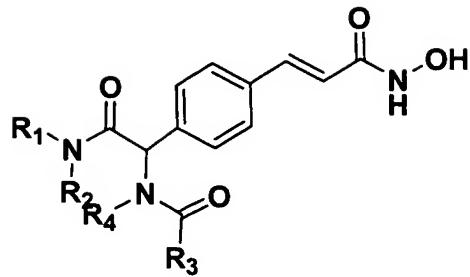
Figure 5A (cont.)

R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	H	3-Phenyl-1-propyl	
PhCH ₂	H	H	Cyclopentyl	Yes
PhCH ₂	H	H	Isoamyl	Yes
PhCH ₂	H	H	R-(+)-a-methylbenzyl	Yes
PhCH ₂	H	H	S-(+)-a-methylbenzyl	Yes
PhCH ₂	H	H	4-Methoxybenzyl	
PhCH ₂	H	H	3-Methoxybenzyl	
PhCH ₂	H	H	4-Aminobenzyl	
PhCH ₂	H	H	2-BenzylPh	
PhCH ₂	H	H	p-MePh	
PhCH ₂	H	H	4-PhenoxyPh	Yes
PhCH ₂	H	H	3-PhenoxyPh	Yes
PhCH ₂	H	H	3-Phenylbenzyl	Yes
PhCH ₂	H	H	2-Phenylbenzyl	Yes
PhCH ₂	H	H	3-NCPh	
PhCH ₂	H	H	4-NCPh	
PhCH ₂	H	H	2-pyridyl	
PhCH ₂	H	H	3-pyridyl	
PhCH ₂	H	H	4-pyridyl	
PhCH ₂	H	H	2,2-Diphenylethyl	
PhCH ₂	H	H	4-PhenylPh	Yes
PhCH ₂	H	H	1-Naphthyl	Yes
PhCH ₂	H	H	1-Naphthalene-methyl	Yes
PhCH ₂	H	H	2-MeO-5-PhenylPh	
PhCH ₂	H	H	m-MeOPh	
PhCH ₂	H	H	p-MeOPh	
PhCH ₂	H	H	1-indanyl	
PhCH ₂	H	H	2-N-Phenylamino-Ph	
PhCH ₂	H	H	4-N-Phenylamino-Ph	
PhCH ₂	H	H	3-pyridylmethyl	
PhCH ₂	H	H	4-pyridylmethyl	

Figure 5A (cont.)

R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	H	3,4-DiMeO-phenethyl	
PhCH ₂	H	H	Phenethyl	Yes
PhCH ₂	H	H	3-pyrazolyl	
PhCH ₂	H	H	Ph	Yes
PhCH ₂	H	H	3-Benzylxy-Ph	
PhCH ₂	H	H	4-Benzylxy-Ph	
PhCH ₂	H	H	2-Aminobenzanilide	
PhCH ₂	H	H	3-Nitrobenzyl	
PhCH ₂	H	H	4-Nitrobenzyl	
PhCH ₂	H	H	m-Nitro-Ph	
PhCH ₂	H	H	p-Nitro-Ph	
PhCH ₂	H	H	3-Chlorobenzyl	
PhCH ₂	H	H	4-Chlorobenzyl	
PhCH ₂	H	H	2-Chloro-Ph	
PhCH ₂	H	H	3-Chloro-Ph	
PhCH ₂	H	H	4-Chloro-Ph	
PhCH ₂	H	H	L-Phenylalaninol	
PhCH ₂	H	H	D-Phenylalaninol	
PhCH ₂	H	H	3-(2-ethyl)indolyl	
PhCH ₂	H	H	p-HO-PhCH ₂ CH ₂ -	
PhCH ₂	H	H	2-(1-pyrrolidyl)ethyl	
PhCH ₂	H	H	Cyclohexyl	

Figure 5B



R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	H	CH ₃	Yes
PhCH ₂	H	CH ₃	CH ₃	
PhCH ₂	H	n-Propyl	CH ₃	Yes
PhCH ₂	H	c-Hexyl	CH ₃	Yes
PhCH ₂	H	MeO(CH ₂) ₂ -	CH ₃	Yes
PhCH ₂	H	Me(CH=CH) ₂ -	CH ₃	Yes
PhCH ₂	H	Ph	CH ₃	Yes
PhCH ₂	H	o-MePh	CH ₃	Yes
PhCH ₂	H	m-MePh	CH ₃	Yes
PhCH ₂	H	p-MePh	CH ₃	
PhCH ₂	H	o-CF ₃ Ph	CH ₃	Yes
PhCH ₂	H	m-CF ₃ Ph	CH ₃	Yes
PhCH ₂	H	p-CF ₃ Ph	CH ₃	Yes
PhCH ₂	H	o-MeOPh	CH ₃	Yes
PhCH ₂	H	m-MeOPh	CH ₃	Yes
PhCH ₂	H	p-MeOPh	CH ₃	Yes
PhCH ₂	H	o-BrPh	CH ₃	Yes
PhCH ₂	H	m-BrPh	CH ₃	Yes
PhCH ₂	H	p-BrPh	CH ₃	Yes
PhCH ₂	H	o-HOPh	CH ₃	Yes
PhCH ₂	H	m-HOPh	CH ₃	Yes
PhCH ₂	H	p-HOPh	CH ₃	Yes
PhCH ₂	H	o-PhOPh	CH ₃	Yes
PhCH ₂	H	m-PhOPh	CH ₃	
PhCH ₂	H	p-PhOPh	CH ₃	
PhCH ₂	H	m-Me ₂ NPh	CH ₃	

Figure 5B (cont.)

R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	p-Me ₂ NPh	CH ₃	
PhCH ₂	H	m-NCPh	CH ₃	Yes
PhCH ₂	H	p-NCPh	CH ₃	Yes
PhCH ₂	H	1-Naphthyl	CH ₃	Yes
PhCH ₂	H	2-Naphthyl	CH ₃	Yes
PhCH ₂	H	p-PhPh	CH ₃	
PhCH ₂	H	m-NO ₂ PhCH=CH-	CH ₃	Yes
PhCH ₂	H	PhCH ₂ CH ₂ -	CH ₃	Yes
PhCH ₂	H	PhCH ₂	CH ₃	Yes
PhCH ₂	H	Ac-D-Pro	CH ₃	Yes
PhCH ₂	H	Ac-L-Pro	CH ₃	Yes
PhCH ₂	H	Ac-D-Phe	CH ₃	Yes
PhCH ₂	H	Ac-L-Phe	CH ₃	Yes
PhCH ₂	H	Ac-D-Try	CH ₃	
PhCH ₂	H	Ac-L-Try	CH ₃	
PhCH ₂	H	2-furyl	CH ₃	
PhCH ₂	H	3-furyl	CH ₃	
PhCH ₂	H	furylCH=CH-	CH ₃	
PhCH ₂	H	2-benzofuranyl	CH ₃	
PhCH ₂	H	1-methyl-2-pyrrolyl	CH ₃	
PhCH ₂	H	4-(1H-pyrrol-1-yl)Ph	CH ₃	
PhCH ₂	H	2-hydroxy-5-(1H-pyrrol-1-yl)	CH ₃	
PhCH ₂	H	2,6-dimethoxypyridyl	CH ₃	
PhCH ₂	H	4-pyridyl	CH ₃	
PhCH ₂	H	3-pyridyl	CH ₃	
PhCH ₂	H	α -hydroxymethyl	CH ₃	
PhCH ₂	H	2-quinolinyl	CH ₃	
PhCH ₂	H	5-methoxy-2-indolyl	CH ₃	
PhCH ₂	H	HO ₂ C(CH ₂) ₆ -	CH ₃	
PhCH ₂	H	4-nitro-3-pyrazolyl	CH ₃	
PhCH ₂	H	4-imidazolyl-CH=CH-	CH ₃	
PhCH ₂	H	(2-pyrimidylthio)CH ₂	CH ₃	
PhCH ₂	H	5-methyl-3-pyrazolyl	CH ₃	
PhCH ₂	H	3-hydroxy-2-quinoxaliny	CH ₃	

Figure 5B (cont.)

R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	2-pyrazinyl	CH ₃	
PhCH ₂	H	H	CH ₃	
PhCH ₂	H	H	Isopropyl	Yes
PhCH ₂	H	H	Ethyl	
PhCH ₂	H	H	3-Phenyl-1-propyl	Yes
PhCH ₂	H	H	Cyclopentyl	Yes
PhCH ₂	H	H	Isoamylamine	
PhCH ₂	H	H	R-(+)-a-methylbenzyl	Yes
PhCH ₂	H	H	S-(+)-a-methylbenzyl	Yes
PhCH ₂	H	H	4-Methoxybenzyl	Yes
PhCH ₂	H	H	3-Methoxybenzyl	Yes
PhCH ₂	H	H	4-Aminobenzyl	Yes
PhCH ₂	H	H	2-BenzylPh	Yes
PhCH ₂	H	H	p-MePh	Yes
PhCH ₂	H	H	4-PhenoxyPh	Yes
PhCH ₂	H	H	3-PhenoxyPh	
PhCH ₂	H	H	3-Phenylbenzyl	Yes
PhCH ₂	H	H	2-Phenylbenzyl	Yes
PhCH ₂	H	H	3-NCPh	Yes
PhCH ₂	H	H	4-NCPh	Yes
PhCH ₂	H	H	2-pyridyl	
PhCH ₂	H	H	3-pyridyl	
PhCH ₂	H	H	4-pyridyl	
PhCH ₂	H	H	2,2-Diphenylethyl	Yes
PhCH ₂	H	H	4-PhenylPh	
PhCH ₂	H	H	1-Naphthyl	Yes
PhCH ₂	H	H	1-Naphthalene-methyl	Yes
PhCH ₂	H	H	2-MeO-5-PhenylPh	
PhCH ₂	H	H	m-MeOPh	Yes
PhCH ₂	H	H	p-MeOPh	Yes
PhCH ₂	H	H	1-indanyl	
PhCH ₂	H	H	2-N-Phenylamino-Ph	Yes
PhCH ₂	H	H	4-N-Phenylamino-Ph	
PhCH ₂	H	H	3-pyridylmethyl	

Figure 5B (cont.)

R1	R2	R3	R4	< 5 μM Activity
PhCH ₂	H	H	4-pyridylmethyl	
PhCH ₂	H	H	3,4-DiMeO-phenethyl	Yes
PhCH ₂	H	H	Phenethyl	Yes
PhCH ₂	H	H	3-pyrazolyl	
PhCH ₂	H	H	Ph	Yes
PhCH ₂	H	H	3-Benzylxy-Ph	Yes
PhCH ₂	H	H	4-Benzylxy-Ph	Yes
PhCH ₂	H	H	2-Aminobenzanilide	
PhCH ₂	H	H	3-Nitrobenzyl	Yes
PhCH ₂	H	H	4-Nitrobenzyl	Yes
PhCH ₂	H	H	m-Nitro-Ph	
PhCH ₂	H	H	p-Nitro-Ph	Yes
PhCH ₂	H	H	3-Chlorobenzyl	
PhCH ₂	H	H	4-Chlorobenzyl	Yes
PhCH ₂	H	H	2-Chloro-Ph	Yes
PhCH ₂	H	H	3-Chloro-Ph	Yes
PhCH ₂	H	H	4-Chloro-Ph	Yes
PhCH ₂	H	H	L-Phenylalaninol	
PhCH ₂	H	H	D-Phenylalaninol	
PhCH ₂	H	H	3-(2-ethyl)indolyl	Yes
PhCH ₂	H	H	p-HO-PhCH ₂ CH ₂ -	
PhCH ₂	H	H	2-(1-pyrrolidyl)ethyl	
PhCH ₂	H	H	Cyclohexyl	Yes